

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (currently amended) A preparation for determining pyrimidine metabolizing activity, comprising ~~[[as an]]~~ at least one active ingredient ~~a pyrimidine compound or its metabolite~~ selected from 5-fluorodihydrouracil, dihydrouracil, dihydrothymine, fluoro- β -ureidopropionic acid, β -ureidopropionic acid, β -ureidoisobutyric acid, in which at least one of C, O and N is labeled with a non-radioactive isotope selected from ^{13}C , ^{18}O and ^{15}N , respectively, ~~the preparation being designed for administering to a subject.~~

Claims 2-6. (canceled).

7. (currently amended) A method for determining pyrimidine metabolizing activity in an individual subject, comprising:

(i) ~~administering to the subject a preparation comprising a pyrimidine compound or its metabolite~~ uracil or thymine wherein at least one of C, O, and N is labeled with a non-radioactive isotope, and measuring a non-radioactive isotope-labeled metabolite; ~~and measuring a non-radioactive isotope-labeled metabolite~~

(ii) administering to the subject dihydrouracil or dihydrothymine wherein at least one of C, O, and N is labeled with a non-radioactive isotope, and measuring a non-radioactive isotope-labeled metabolite;

(iii) administering to the subject β -ureidopropionic acid or β -ureidoisobutyric acid wherein at least one of C, O, and N is labeled with a non-

radioactive isotope, and measuring a non-radioactive isotope-labeled metabolite;

and

(iv) determining pyrimidine metabolizing activity in the subject from the measurements of steps (i), (ii), and (iii).

8. (currently amended) A method according to claim 7, wherein ~~the measuring comprises measuring the non-radioactive isotope-labeled metabolite~~ in (i), (ii), and (iii) is excreted from the body.

9. (currently amended) A method according to claim 8, wherein the non-radioactive isotope-labeled metabolite in (i), (ii), and (iii) is isotope-labeled CO₂, and the measuring comprises measuring the isotope-labeled CO₂ excreted ~~in the~~ as expired air.

10. (currently amended) A method according to claim 7, wherein the pyrimidine metabolizing activity to be determined is ~~an activity of at least one pyrimidine metabolizing enzyme selected from dihydropyrimidine dehydrogenase, dihydropyrimidinase and β -ureidopropionase.~~

11. (currently amended) A method according to claim 7, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject in (i), (ii), and (iii) is compared with the measurement from a healthy subject.

12. (currently amended) A method according to claim 8, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject in (i), (ii), and (iii) is compared with the measurement from a healthy subject.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

13. (currently amended) A method according to claim 9, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject in (i), (ii), and (iii) is compared with the measurement from a healthy subject.

14. (currently amended) A method for ~~establishing~~ determining a dosage regimen of a pyrimidine drug ~~for an individual subject~~, comprising:

administering to the subject a preparation comprising a pyrimidine compound or its metabolite wherein at least one of C[~~[,]~~] and O, ~~and N~~ is labeled with a non-radioactive isotope ¹³C and ¹⁸O, respectively;

measuring a non-radioactive isotope-labeled metabolite CO₂ excreted as expired air to assess pyrimidine metabolizing activity in the subject; and

determining the dosage regimen based on the assessed pyrimidine metabolizing activity.

15. (previously presented) A method according to claim 14, wherein the pyrimidine drug is a fluorouracil drug selected from 5-fluorouracil, tegafur, carmofur and doxifluridine.

16. (previously presented) The method according to claim 14, wherein the pyrimidine metabolizing activity to be determined is an activity of at least one pyrimidine metabolizing enzyme selected from dihydropyrimidine dehydrogenase, dihydropyrimidinase and β -ureidopropionase.

17. (previously presented) The preparation according to claim 1, wherein the preparation has an oral dosage form.

18. (canceled).

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

19. (currently amended) The preparation according to claim 17 1, wherein at least one of C and O is labeled with ~~a non-radioactive isotope~~ ^{13}C and ^{18}O , respectively, and the preparation is designed for measuring a non-radioactive isotope-labeled CO_2 excreted ~~in the~~ as expired air after oral administration.

20. (new) The method according to claim 7, wherein at least one of C and O is labeled with ^{13}C and ^{18}O , respectively.

21. (new) A method for determining pyrimidine metabolizing activity in an individual subject, comprising:

- (i) administering to the subject dihydrouracil or dihydrothymine wherein at least one of C, O, and N is labeled with a non-radioactive isotope, and measuring a non-radioactive isotope-labeled metabolite;
- (ii) administering to the subject β -ureidopropionic acid, β -ureidoisobutyric acid wherein at least one of C, O, and N is labeled with a non-radioactive isotope, and measuring a non-radioactive isotope-labeled metabolite; and
- (iii) determining pyrimidine metabolizing activity in the subject from the measurements of steps (i) and (ii).

22. (new) A method according to claim 21, wherein the non-radioactive isotope-labeled metabolite in (i) and (ii) is excreted from the body.

23. (new) A method according to claim 22, wherein the non-radioactive isotope-labeled metabolite in (i) and (ii) is isotope-labeled CO_2 , and the measuring comprises measuring the isotope-labeled CO_2 excreted as expired air.

24. (new) A method according to claim 21, wherein the pyrimidine metabolizing activity to be determined is dihydropyrimidinase.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

25. (new) A method according to claim 21, wherein the pyrimidine metabolizing activity to be determined is B-ureidopropiohase.

26. (new) A method according to claim 21, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject in (i) and (ii) is compared with the measurement from a healthy subject.

27. (new) A method according to claim 22, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject (i) and (ii) is compared with the measurement from a healthy subject.

28. (new) A method according to claim 23, wherein the measurement of the non-radioactive isotope-labeled metabolite from the subject (i) and (ii) is compared with the measurement from a healthy subject.

29. (new) The method according to claim 21, wherein at least one of C and O is labeled with ^{13}C and ^{18}O , respectively.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com